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Title: The effect of time to primary repair on final visual outcome after open globe injury

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Synopsis

When primary repair is delayed beyond 24 hours after open globe injury, presenting visual acuity and time from injury to repair are the strongest predictors of outcome, independent of the development of endophthalmitis.

Abstract

Background/Aims: Historic data suggests that open globe injuries should be repaired within 12-24 hours to reduce the risk of endophthalmitis. However, endophthalmitis is uncommon when systemic antibiotic prophylaxis is given. It is not clear whether delayed primary repair impacts visual outcomes in other ways or what is the optimum time to repair. We aimed to examine the effect of time to primary repair on visual outcomes.

Methods: Retrospective comparative case series, including all open globe injuries presenting to the Birmingham Midland Eye Centre between 1st Jan 2014 and 15th Mar 2016. Presenting features, mechanism of injury, 6-12 month visual acuity and demographic data were examined.

Results: 56 open globe injuries were repaired, of which sufficient data for analysis was available on 52 cases. The mean time to primary repair was 1 day after injury (range 5 hours to 7 days). Final visual acuity at 6-12 months was related to the presenting visual acuity and ocular trauma score and to the time between injury and primary repair, with a reduction in predicted visual acuity of logMAR 0.37 for every 24 hours delay (95% CI 0.14-0.6).

Discussion: Open globe injuries should be repaired promptly. Presenting visual acuity remains the strongest predictor of outcome, however, delay to primary repair also reduced final visual acuity and any significant delay from injury to repair is likely to negatively impact final visual outcome.

The estimated annual incidence of open globe injuries in the industrialised world is 3.5/100 000[1] Open globe injury causes significant visual loss in the civilian population, but is more common in the military, where 5-10% of all cases of major trauma involve the eye.[2] Injury severity may be assessed using the Ocular Trauma Score (OTS) or the Classification and Regression Tree (CART) classification systems, both of which predict some of the variability in visual outcomes.[3, 4]

Complications of open globe injury include endophthalmitis, retinal detachment, cataract, corneal scarring, proliferative vitreoretinopathy, phthisis and irreparable injury requiring evisceration or enucleation. In historic studies, the risk of endophthalmitis is increased when primary repair is performed more than 24 hours after injury,[5] or more than 12 hours in a recent series.[6] However, military case series in which intraocular foreign body (IOFB) removal and, in some cases primary repair, was delayed far beyond 24 hours suggest that even with retained organic IOFB, endophthalmitis is uncommon if broad spectrum systemic antibiotic prophylaxis is given.[7, 8]

In one large Brazilian case series, delays to primary repair greater than 24 hours increased the odds of a poor outcome in patients without endophthalmitis by 1.16,[9] though other studies did not associate delayed repair with a clinically meaningful change in outcome.[10] In a series of military injuries, delays to primary repair of more than 24 hours increased the odds of a poor outcome by 1.69, though this was borderline significant (p=0.08).

There is therefore some evidence that primary repair should not be delayed beyond 24 hours, but the magnitude of that effect is not defined. The practice in our centre is to offer emergency ophthalmic surgery between 0900 and 1900 hours only. We therefore have a range of times to primary repair from a few hours after injury to several days where other factors delay repair.

We aimed to study the relationship between the delay from open globe injury to primary repair and the visual outcomes in patients repaired in our centre.

METHODS

The study was approved by the Clinical Governance Department of the Sandwell and West Birmingham Hospitals NHS Trust.

We studied a retrospective comparative consecutive case series. We included all open globe injuries presenting to the Birmingham Midland Eye Centre, a major UK tertiary referral eye unit, between 1st Jan 2014 and 15th Mar 2016. Cases were identified from the emergency operating theatre logs.

We recorded the presenting features including presenting best-corrected visual acuity (VA), presence of an afferent pupillary defect and endophthalmitis, the injury classification according to the Birmingham Eye Trauma Terminology System,[11] mechanism of injury, demographic data including age, multiple index of deprivation (IMD) score derived from postcode data, working pattern at the time of repair, surgeries performed and visual outcomes in terms of VA.[12] Working pattern at the time of repair was taken as the time at which surgery started, classified as: normal working day (NWD; 9am-5pm Monday to Friday), evening (after 5pm Monday to Friday) and weekend (Saturday and Sunday). Surgery was considered out-of-hours when started in the evening or the weekend. Secondary procedures were considered as any surgical procedure, directly related to the trauma, performed after the time of primary repair. Because of the problems associated with recording final VA with variable time to follow up we recorded the best-corrected VA between 6 and 12 months after injury, using the closest measurement to 12 months where more than one result was available and this is referred to as final VA. VA measurements were converted to logMAR equivalents for analysis, including those less than 20/1200, as previously described.[8] Time of repair was recorded as the time at which primary repair was completed.

Statistical analyses wereconducted in R,[13] (www.r-project.org) using the rms and mice packages.[14, 15] Average values are displayed as mean ± estimated population standard deviation. To examine the relationship between injury severity, time between injury and primary repair and visual outcomes, we performed linear regression analysis with sequential addition of the predictors: presenting VA; time to repair; OTS. Student's t-test and 1-way ANOVA were used for comparisons

between two and three groups respectively. Sensitivity analysis used multiple imputation with a chained equations method (with 10 imputed datasets) to assess the impact of missing values.

RESULTS

Fifty six consecutive open globe injuries were included, of which 52 cases had sufficient follow-up data for analysis. All were unilateral. The mean time to primary repair was 24.2±26.9 hours after injury (range 5 hours to 7 days). Twenty six were penetrating injuries (46.4%), seven had IOFB (12.5%) and 23 (41.1%) were ruptures. Patient demographics and injury mechanisms are summarised in Table 1.

Mechanism of Injury	Number of patients (%)	Mean patient age (Std dev)	Number male (%)	Mean IMD score (Std dev)
Domestic injury	35 (63)	53.7 (24.3)	25 (71)	27.3 (17.0)
Blunt object	8 (14)	57.2 (21.2)	5 (63)	20.3 (11.3)
Sharp object	15 (27)	38.5 (17.7)	15 (100)	27.5 (17.7)
Fall	12 (21)	70. (22.5)	5 (42)	31.6 (18.8)
Assault	8 (14)	44.2 (22.9)	6 (75)	46.6 (22.1)
Blunt object	6 (11)	48.4 (25.4)	5 (83)	39.1 (19.6)
Sharp object	2 (3.6)	31.5	1 (50)	68.80
Work-related	7 (13)	47.9 (16.9)	5 (71)	15.6 (9.73)
Blunt object	4 (7.1)	44.1 (20.4)	3 (75)	16.8 (11.6)
Sharp object	3 (5.3)	53.0 (12.6)	2 (67)	14.1 (8.72)
Other	1			
Unknown mechanism	5 (8.9)	23.4 (19.1)	4 (80)	32.1 (16.2)

Table 1. Patient demographics and injury mechanisms. Std dev, standard deviation; IMD, index of multiple deprivation.

Time to repair

Forty two cases were repaired less than 24 hours after injury and 10 more than 24 hours. Fitting a linear regression model to the data explained a high proportion of variance in final VA (Fig. 1; R^2=0.74). We modelled OTS as a five point categorical variable; however, for illustrative purposes, the difference in outcomes between an initial OTS of 1-3 compared to 4-5 is an increase in final VA of logMAR 2.20 (Fig. 1A; 95% CI: 1.10-3.29; p=0.0002). For time to repair, every 24 hours of delay

was associated with an increase in logMAR final VA of 0.37 (Fig. 1B; 95% CI 0.14-0.6; p=0.0028). There was also a strong association between presenting VA and final VA, with an increase of logMAR 1 in presenting VA associated with an increase of logMAR 1.77 in final VA (Fig. 1C; 95% CI 1.16-2.38; p<0.0001). The significance of including each term in the model, when tested sequentially using ANOVA was: presenting VA, p<0.0001; time to repair, p=0.077; OTS, p=0.0006. Age, gender, IMD score and working pattern at the time of repair did not add significant explanatory value to the model.

When two cases who developed endophthalmitis were excluded from the analysis, presenting VA (p<0.001) and time to repair (p=0.04) remained significant predictors of final VA, but OTS no longer demonstrated a statistically significant association (p=0.49).

When the analysis was limited to cases repaired less than 24 hours after presentation, only presenting VA remained a significant predictor of final VA (p<0.001), whilst time to repair (p=0.75) and OTS (p=0.48) did not demonstrate any relationship with final VA in this subgroup.

Sensitivity analysis using multiple imputation of missing values with pooled analysis of the 10 imputed datasets yielded results consistent with the primary analysis. For time to repair, every 24 hours of delay was associated with an estimated increase in logMAR final VA of 0.292 (95% CI 0.054-0.529; p=0.017). An increase of logMAR 1 in presenting VA was associated with an estimated increase of logMAR 1.548 in final VA (95% CI 0.867-2.228; p<0.0001). Considering OTS as a binary variable (as above), the estimated difference in final VA between an OTS of 1-3 and 4-5 is an increase of logMAR 1.629 (95% CI: 0.525-2.734; p=0.005).

Compared to cases repaired more than 24 hours after injury, cases repaired less than 24 hours after injury presented sooner after injury (5.34±4.84 vs 35.6±50.2 hours; p=0.06), were older (50.7±24.5 vs 41.4±23.5 years; p=0.43) and had similar IMD scores (30.3±19.1 vs 28.9±18.6) and presenting VA (logMAR 2.22±1.27 vs 2.11±1.38; p=0.68) and OTS (2.73±1.42vs2.89±1.31; p=0.42). Cases presenting

less than and more than 24 hours after injury had similar times between presentation and surgery (12.0±9.05 vs 14.5±8.12 hours; p=0.60).

Endophthalmitis

Two patients developed endophthalmitis before presentation, which was at 32 and 26 hours after injury, leading to final VA of logMAR 2 and 1.18 respectively. No patients developed new signs of endophthalmitis after presentation. It is standard practice in our centre to give oral ciprofloxacin to open globe injuries, but this was not well documented, so it is not possible to state reliably what proportion of patients received antibiotic prophylaxis.

Secondary procedures

Eight patients required delayed vitreoretinal surgery. Two patients developed funnel retinal detachment after primary repair and vitreoretinal surgery was deemed to be futile. Of six patients with IOFB, three had IOFB removal at the time of primary repair, one of whom required repeat vitreoretinal surgery, initially having Bacillus cumulus endophthalmitis and subsequently developing a PVR detachment under silicone oil that was treated with retinectomy and heavy oil (final VA logMAR 2). Five patients underwent delayed lens extraction, 3 patients had secondary IOL insertion. Four patients required secondary evisceration. No eyes were primarily eviscerated or enucleated.

The mean presenting OTS and final VA were similar between patients who underwent secondary vitreoretinal surgery (OTS 2.56; final VA logMAR 1.98) and patients who did not (OTS 2.82 p=0.60; logMAR 1.25; p=0.17).

Out-of-hours surgery

In 22 cases, repair was started in the NWD, 19 cases were repaired on weekday evenings and 14 at weekends (Fig. 2A). The visual outcome did not vary by working pattern at the time of repair with

mean final VA of logMAR 1.31±1.51 for cases repaired in the NWD, 1.21±1.53 in the evening and 1.59±1.25 at the weekend (p=0.471; OTS 2.64±1.47, 3.11±1.29, 2.64±1.15 respectively).

Forty eight percent of all open globe injuries repaired between Monday and Friday were done in the evening, whereas 0% of weekend repairs were in the evening (Fig. 2A; p=0.002, Fisher's exact test). Cases repaired in the evening had a mean time between presentation and surgery of 7.19±5.79 hours compared to 14.91±10.8 for those repaired in the NWD and 15.18±6.67 at weekends (Fig 2B; p=0.02, 1-way ANOVA). However, the total time between injury and repair did not differ significantly between NWD, evenings and weekends being 26.5±33.1, 21.4±27.7 and 25.4±12.3 respectively (Fig. 2B; p=0.835. 1-way ANOVA).

DISCUSSION

Our data provides evidence for an association between time to primary repair and VA at 6-12 months after injury and demonstrates that delays of 24 hours are associated with measurable reductions in VA. The magnitude of the effect appears to be a worsening of logMAR 0.37 for every 24 hours of delay, equivalent to the loss of two to three lines on a Snellen chart.

This is retrospective data, so unmeasured confounders cannot be excluded. Unsurprisingly, delayed presentation was associated with an overall delay to repair. Late presentation is expected to be associated with endophthalmitis,[5] which was the case in our series, but the relationship between time to repair and outcome remained significant even when the endophthalmitis cases were excluded, suggesting that other consequences of the delay to surgery rather than infection explains this relationship. The similarity in time between presentation and repair for early and late presenters, suggests that treatment is not prioritised differently in cases that present late. One might also expect delayed presentation to be associated with reduced educational level, but there was no evidence of a relationship between IMD and time to presentation in our data. Surgical delay may also be a clinical decision to afford better conditions for repair of complex injuries or give lower

priority to less severe injuries. Neither better conditions for repair nor less severe injuries are likely to prejudice outcomes and there was no difference in OTS between injuries repaired sooner or later Patients repaired later were younger than those repaired sooner, and it seems unlikely that increasing age could confound our findings by having a positive influence on outcome, which would be the opposite effect to that seen in traumatic brain injury and we found no effect of including age in the regression model.[16]

Previous retrospective studies report that endophthalmitis start to increase after 12-24 hours and the probability of a good visual outcome declines when repair is delayed more than 24 hours after injury.[5, 6, 9, 10]. However, systemic antibiotic prophylaxis reduces the risk of endophthalmitis and the magnitude of other effects of delay on final VA has not been reported.[7] Eyes may be potentially viable even when primary repair is delayed for as long as 21 days,[17] though in this case series the injury severities and the detailed effects of such delays were not reported. Our data is in line with previous studies, but goes further to show that the magnitude of the effect of delaying surgery by 24 hours is between logMAR 0.14 and 0.6, equivalent to between one and four Snellen lines, compared to immediate repair, whilst a delay of 48 hours is associated with a greater average reduction of logMAR 0.74. It should be noted though, that increased delay is associated with a linear increase in the uncertainty of the regression model, so the 95% confidence interval at 48 hours for the increase in logMAR final VA is 0.27-1.22.

The time of day at which repair was conducted did not affect visual outcome in our series, suggesting that our on call arrangements, in which senior trainees (with 5 or more years of ophthalmic surgical experience) cover out-of-hours work, do not adversely affect patient outcomes. Cases operated in the evening are expected to have a shorter time to surgery compared to patients operated in the NWD because the latter may have presented overnight or the previous evening. However, the disparity in evening operating between weekdays and the weekends, suggests either a

hidden barrier to emergent operating in the weekend evenings or preferential scheduling into the weekday evenings.

An understanding of the impact of delayed primary repair on patient outcomes is important to planning hospital eye services in the civilian environment where “on call” surgical capacity is often significantly limited compared to the NWD and work in the NWD competes with elective surgery. It is also relevant to planning the provision of ophthalmic care to the military environment where deployed assets are limited compared to those available at hospitals in the home country and evacuation timelines may be several days. The number of cases is relatively small and the association between delayed repair and visual outcome is weak. These results would therefore benefit from confirmation in a larger cohort. However, the cumulative strength of this and other published data and the lack of conceivable disadvantages of early repair would make it unethical to definitively answer the question by conducting a randomised trial intentionally delaying repair. Whilst this paper provides evidence on the magnitude of the effect of delaying repair, limited information is provided on the effects of surgical environment, surgeon’s experience or surgical team, which may also be trade-offs engendered by a decision to repair a globe urgently, such as overnight in an emergency theatre by “on call” staff compared to repair on an elective theatre list the next day, though our data suggests that these effects are not significant in our current surgical set-up. When planning ophthalmic emergency services it is important that provisions are made for prompt primary repair, but until evidence exists on the effects of other factors it is also important that the surgical environment and equipment are not compromised.

COMPETING INTERESTS

The authors have no competing interests.

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CONTRIBUTORSHIP

RB and PM conceived and designed the study. RB acquired the data. RB and JB analysed and interpreted the data. RJB drafted the final manuscript and all authors revised it critically for important intellectual content and gave final approval of the version to be published. All authors agree to be accountable for all aspects of the work in ensuring that any questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Figure legends

Figure 1: Visualisation of the model-based effects of each predictor by plotting fitted values. **A**. The effect of OTS. Patients with an OTS in categories 1, 2 and 3 exhibit similar levels of final VA, whereas those with an OTS in categories 4 and 5 exhibit levels of final VA 2.20 higher (95% CI: 1.10-3.29; p=0.0002). **B**. Time to repair. An increase of 1 unit in time to repair is associated with an increase of 0.37 (95%CI: 0.14 - 0.60) units in final VA. **C**. Presenting VA has a strong association with final VA with an increase of 1 unit in presenting VA associated with an increase of 1.77 (95%CI: 1.16 - 2.38) units in final VA.

Figure 2. Cases analysed by working pattern at the time of repair. **A**. Approximately half of all weekday cases were repaired in the NWD and half in the evening. The proportion repaired at weekends (25.5%) is similar to that expected (28.5% of the week), however, no cases were repaired in the evening at weekends, which is significantly less than expected (p=0.002). **B**. Cases repaired in the evening were repaired significantly sooner after admission than either cases repaired in the NWD or at weekends (p=0.02), however, the total time between injury and repair was similar for cases repaired at different times of day.

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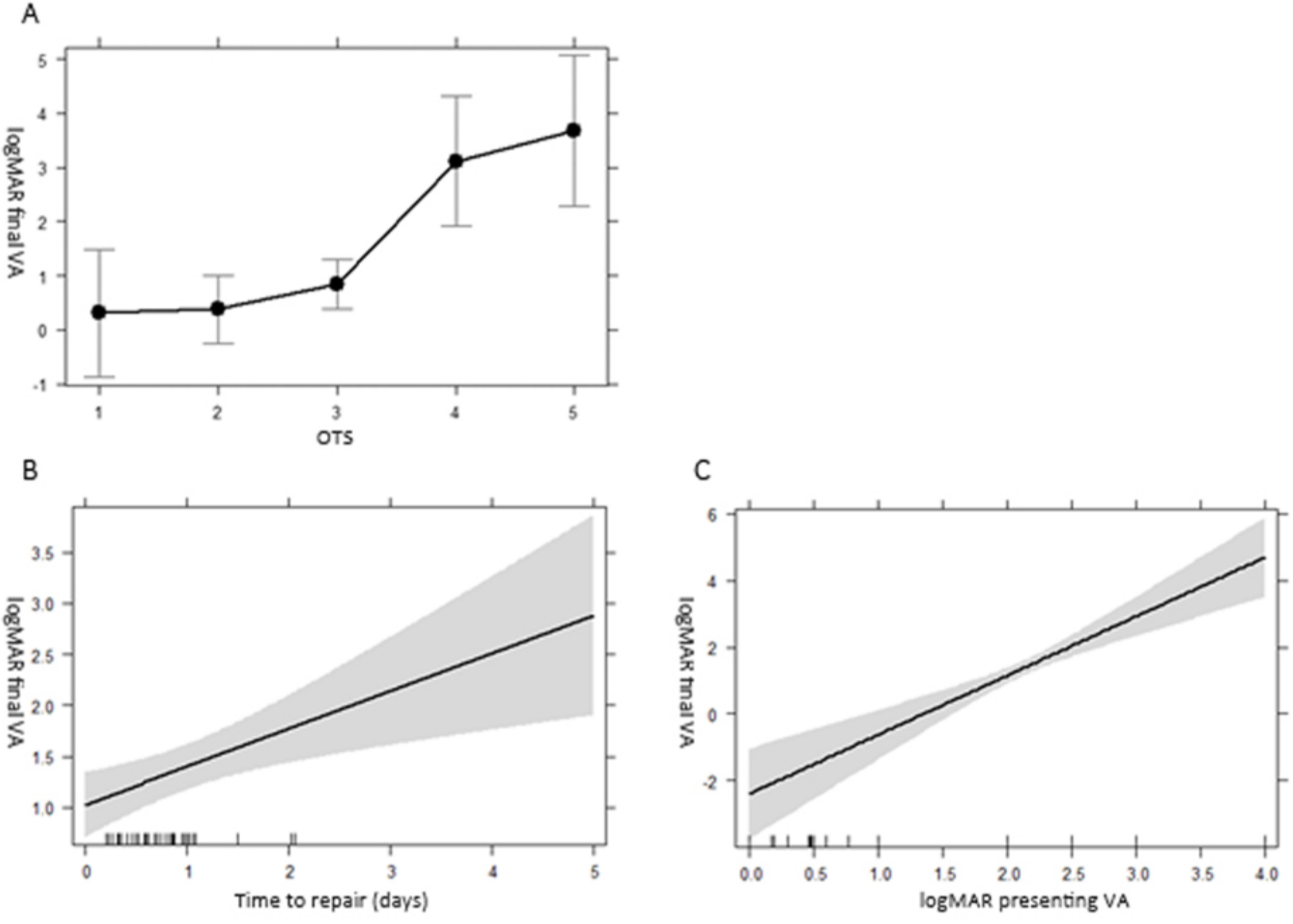
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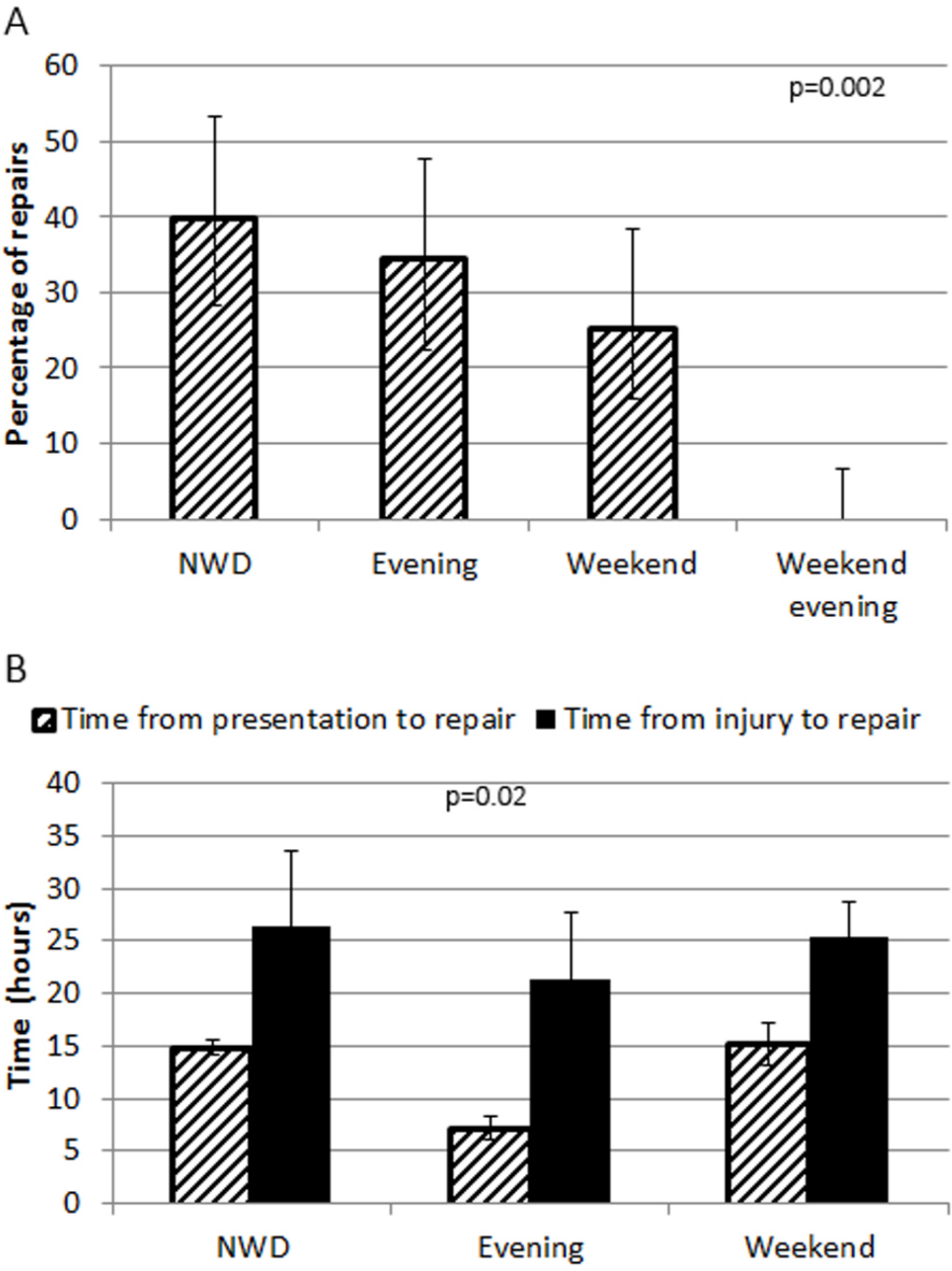
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